Remarks to the Amendments

The status of claims 1, 3, 9-13, 17, 24, 25, and 86-94 is given as being the original claims. All other claims have been withdrawn. Applicants have voluntarily withdrawn Claims 11-13 and 15 because current prosecution is focused on spinocerebellar ataxia type 1. Claim 1 has been amended.

Claim 1 was amended to remove periods found internally in the claim. These were replaced by brackets following each subgroup ((a), (b), (c), and (d)). Claim 1 has been amended to remove internal periods found in the claims and replaces them with parenthesis, and to insert that the claim system of treatment specifically relates to treatment of patients. The specification is replete with reference to a patient. The term "patient" is defined on page 9, third paragraph of the specification.

Applicants have withdrawn Claim 23 to the more broadly drawn group of sequences, and submit new claims 85-89:

- Claim 85 is drawn to siRNAs which inhibit expression of ataxin-1. Support for claim the "inhibition of expression" of ataxin-1 is defined on page 12 first full paragraph of the specification, and elsewhere in the specification.
- Claim 86 is drawn to siRNAs which inhibits the activity of ataxin-1. Support for claim the "inhibition of expression" of ataxin-1 is defined on page 12 first full paragraph of the specification, and elsewhere in the specification.
- Claim 87 is drawn to siRNAs which inhibit levels of ataxin-1 mRNAs. Support a claim that "inhibits the activity" of ataxin-1 is defined starting on the last paragraph on page 11 of the specification, and elsewhere in the specification.
- Claim 88 is drawn to siRNA of sufficient length that comprises any one of SEQ ID Nos; 1-6, 13 or 16. Support for claim the siRNA "of sufficient length" of ataxin-1 is defined in the specification on page 14, last paragraph, and elsewhere in the specification.
- Claim 89 is drawn to siRNAs that are able to stably interact with the ataxin-1 mRNA. Support for claim to siRNAs that "stably interact" of ataxin-1 is defined in the specification on page 14, last paragraph, and elsewhere in the specification.

Applicants' Response

The Examination mailed October 4, 2005 has several objections and rejections to the specification and claims. Applicants reply to each section and item raised by the Examiner in the order they were raised by the Examiner.

Election/Restriction

Applicants affirm the election to prosecute Group IV, Claims 5 and 9-25 drawn to medical systems for treating spinocerebellar ataxia type 1, and the election of a single mRNA target, SCA1, which codes for ataxin 1 protein, and a single small interfering RNA sequence provided for in SEQ ID Nos: 1 and 2. Applicants on their own have withdrawn Claims 11-13 and 15 directed to other target tissues not directly related to spinocerebellar ataxia type 1.

Status of the Application

Claims 1-84 are pending. After entry of applicant's amendments, Claims 2, 3, 4, 11-13, 15-18, 20-22, and 26-84 are withdrawn. Claim 1 is considered to be a linking claim. Therefore, Claims 1, 5, 9-10, 14, and 23-25 are being currently prosecuted.

Priority

Applicants direct the attention of the Examiner to the request for priority that was submitted at the time they filed the instant application. That request was present in the combined declaration and power of attorney to provisional applications 60/444,614 (filed February 3, 2003) and 60/429,387 (filed November 26, 2002).

Verification of applicants request for priority is provided on the USPTO Filing receipt (copy enclosed herewith). Applicants have formally added their priority information on the substitute specification enclosed herewith.

Claim Objections

Claim 1 was objected to because it contain several periods.

Applicants have submitted amendments to claim 1 to remove/replace the extra periods found in the claims.

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Claims 1, 5, 9-15, 19, and 23-25 were objected to because the claim appears to be drawn to a medical device or apparatus, yet the preamble recites a medical "system," which may refer to an apparatus or a method. The Examiner cites The American Heritage Dictionary, 3rd ed. for the definition of a system as being a group of interactions, interrelated elements and as an organized procedure or method, and as such it is not clear what statutory class is intended.

Applicants traverse the Examiner's presumption. First, it appears there is no confusion as it is indicated by the Examiner that none of the steps recite method steps. As far as it being a statutory class, Applicants searched U.S. issued patent having the claim language "system comprising ". The Examiner will be interested to note we found over 250 thousand issued U.S. patents having the sequential terms "system comprising" in the claims. Applicants also searched for words in the order specified of "system" then "comprising", but only required that these terms appear sequentially and that these two words are within 5 words of each other. The Examiner will be interested to note that Applicants found over 400 thousand issued U.S. patents with these criteria. Clearly it is not the policy of the U.S. patent office to restrict patentees from having system claims, and thereby, Applicants respectfully request the present objection be removed.

Double Patenting

The present application was given a provisional obviousness-type double patenting rejection over co-pending application USSN 10/962,732.

Applicants have argued in the rejections under 35 U.S.C § 103 provided herein the teachings of Paxinos et al. (2001) and Cahill et al. (1995) as not being equivalent to Applicant's mapping means.

First, Applicants query the Examiner as whether it is appropriate to make a provisional obviousness-type double patent rejection over a co-pending application which is done in further view of additional art cited. Applicants are not certain whether this is a proper rejection.

Assuming such rejection is proper, but before discussing the relevance of the anatomical and coordinate maps of Paxinos et al., and Cahill et al., Applicants have submitted amendments to Claim 1 to introduce into several locations that we are referring to treating specific location in the brain of a patient, and that the siRNAs are delivered to this location. These amendments help further distinguish the present invention over the teachings of Paxinos and Cahill.

The Examiner sites the anatomical maps of Paxinos and Cahill as a "mapping means," enabling the skilled artisan to locate predetermined locations of the brain. While the map is a useful teaching tool in gross anatomy, such maps can be applied to dissected brains of cadavers, but are only a starting point for mapping a patient's brain. Moving from a generalized anatomical map, such as Paxinos and Cahill falls short in real life. Placing a delivery device into the live brain of a patient requires exquisite preciseness that can not be obtained from just looking at the Maps and coordinates of Paxinos and Cahill. Applicants mapping means is related to precise live coordinates and structures in a patient that are generated for each individual brain. As you may know, there is an infinite variation of head sizes, shapes, and brain anatomy. Applicant's mapping means is tied to live mapping systems of a

patient's brain. The cited maps and coordinates therefore of Paxinos and Cahill fall short of the mark in context of the whole claim.

Applicants respectfully request removal of the present obviousness type double patenting rejection based on (1) that such a rejection in view of additional cited art is improper, and alternatively (2) that on the merits Paxinos and Cahill fail to teach Applicants mapping means if combined with any other references.

Claim Rejections under 35 USC § 112

Claim 23 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 23 recites "a medical system of claim 1 wherein said small interfering RNA is substantially provided for in any one of SEQ ID Nos: 1-44." In response to the previous restriction requirement, applicant elected SEQ ID Nos: 1 and 2. The phrase "substantially provided for in any one of" was regarded by the Examiner as confusing because the metes and bounds of the claim cannot be determined. The Examiner suggests the claim be amended to a more precisely defined siRNA. The examiner also notes the objection to word "system" found in the claim, and was also requested to remove recitations of non-elected inventions SEQ ID Nos: 3-44.

Applicants have withdrawn Claim 23 to the more broadly drawn group of sequences, and submit new claims 85-89. Claim 85 is drawn to siRNAs which inhibit expression of ataxin-1. Claim 86 is drawn to siRNAs which inhibits the activity of ataxin-1. Claim 87 is drawn to siRNAs which inhibit levels of ataxin-1 mRNAs. Claim 88 is drawn to siRNA of sufficient length that comprises any one of SEQ ID Nos; 1-6, 13 or 16. Claim 89 is drawn to siRNAs that are able to stably interact with the ataxin-1 mRNA.

Applicants have previously indicated the support in the specification for the addition of Claims 86-89. In view of withdraw of Claim 23, and the support for Claims 85-89, Applicants respectively request the present rejection be withdrawn.

Claim Rejections under 35 USC § 103

To help with organization in this section, Applicants have summarized the Examiner's arguments using single spaced italics. Applicants' response uses one and one-half spacing of lines with normal font.

Claims 1 and 11-15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (2002); in view of Driscoll et al. (WO 01/49844); Paxinos et al. (2001); and Cahill et al. (1995). The Examiner contends it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Xia et al., Driscoll et al., Paxinos et al., and Cahill et al. to inhibit a specific gene target associated with a particular neurodegenerative disorder using an siRNA-encoding vector, as taught by Xia et al. and Driscoll et al. and then by using the stereotaxic coordinates provided by Paxinos et al. and detailed illustrations shown by Cahill et al., so that said vectors of Xia et al. and Driscoll et al. could be used in a directed delivery system to transmit small interfering RNA (e.g., shRNA) to particular brain cells in specific regions of the brain afflicted by the neurodegenerative disease.

The Examiner indicates that the motivation to create and use such vectors comes from Xia et al., because Xia et al. teaches that such vectors work to reduce endogenous gene expression and because RNA interference is taught by Xia et al. and Driscoll et al. as having the potential to relieve symptoms associated with the neurodegenerative disorders. The Examiner indicates that one would have a reasonable expectation of success given that Driscoll et al. expressly describes methods and examples for constructing and using shRNA expression vectors for purposes of inhibiting the expression of genes associated with neurodegenerative diseases, and that one of skill in the art would therefore have a reasonable expectation of success in predetermining a specific location in the brain, given the maps of Paxinos et al., and the stereotaxic coordinates of Cahill, and the specific working example of Xia et al.

Applicant respectively traverses. Applicants distinguish several aspects of their invention from the teachings of the cited references.

First, the Examiner uses the fact that Xia uses a syringe to deliver the viral vectors containing green fluorescent protein is the equivalent of the delivery means. The Examiner uses the fact that Xia uses a dsRed expression cassette, which allows for unequivocal localization of the injection by fluorescence microscopy as being equivalent to the "mapping means." The problem is that the mapping means of Xia et al. is generally only for sacrificed patients. In Xia et al., the mice have been sacrificed and are now subject to histology. Xia et al. does not provide an active mapping means to determine delivery of live patients and hence could not be used to treat a neurodegenerative disorder. The mapping means of Xia et al. is post-mortem.

The Examiner indicates that Xia shows reduced GFP expression in the injected hemisphere and thus teaches a system for reducing gene expression in the brain using a vector encoding a small interfering RNA. However, as the Examiner well knows, obvious to try is not the standard. Further, the ability to demonstrate suppression of one gene target does not predict that one can reduce the expression of another target. Xia et al tested their siRNAs in neural PC12 cell line based on *in vitro* suppression of a eGFP-polyglutamine fusion vector. It is important to point out that Xia et al. did not measure direct inhibition against the native target, but against an artificially expressed eGFP-polyglutamine fusion sequence. One skilled in the art would not necessarily equate the two.

Based on the demonstrated results of Xia et al., further application of this work more broadly is nothing more than a wish or desired goal – the key words "would be" provide very little guidance as how to make or achieve this goal. It should be pointed out that some of Xia's et al. speculations are also incorrect. Xia et al. incorrectly speculated that they would get better suppression of beta-glucuronidase in HeLa cells if they used siRNA targeting "mRNA accessible sequences." Since the publication of their paper, further developments have shown that "accessibility" of the targeted region of the mRNA is highly questionable, and this issue remains controversial among experts (see Heale BS, Soifer HS, Bowers C, Rossi JJ., Nucleic Acids Res. 2005 Feb 18;33(3):e30.). False speculation brings

into question which speculations should one skilled in the art believe and which ones should they not believe in the literature?

The Examiner uses the Driscoll reference for teaching methods for making and using vectors encoding short hairpin RNAs targeting genes associated with neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease as shown in Figures 4 and 5. Figures 4 and 5 teach using a 1.4 or 1 kilobase insert of the gene to express antisense RNA. Such a teaching actually teaches away using siRNAs. One skilled in the art would not know from reading Driscoll where one should target the siRNAs. Figures 4-5 of Driscoll teaches targeting a ~1 killobase DNA insert for RNA for suppression. Although the focus of the present set of claims is directed to ataxin-1, Applicants note for the Examiner Figure 4 of Driscoll teaches suppression against the expression of the beta-amyloid protein (APP), which in Applicants opinion is the wrong way to treat Alzheimer's disease. By inhibiting APP one is inhibiting a critical protein which is not necessarily something one skilled in the art wants to do when treating a patient. What one wants to inhibit is abnormal processing of APP, but not APP itself. The importance here for ataxin-1 and treatment of SCA1, is that the potential significance of this reference has to be carefully reconsidered. Furthermore, the only thing shown in Driscoll is schematic drawings of vectors. Nothing shown in Driscoll actually demonstrates effectiveness against the target, and those approaches appear dubious in view of the state of the art. Driscoll teaches building expression cassettes for treating Alzheimer's disease using 1.4 kilobase antisense RNA to APP. Nothing in the Driscoll reference gives any predictive ability that this actually works against the neurodegenerative target or that it brings about a positive therapeutic outcome, let alone do Applicants believe APP is a correct target. Use of 1.4 kilobase antisense mRNAs also has the problem of not being able to necessarily control the specificity of smaller sequences contained in such a large portion of antisense RNA.

Taken together, Xia et al (2002) and Driscoll (WO 01/49844) teach a CONTRADICTION. Xia clearly states (in the introductory paragraphs) that "In mammalian cell culture, siRNA-mediated reduction in gene expression has also been accomplished by transfecting synthetic RNA oligonucleotides or plasmids, with

the requirement that fragments be <30 base pairs to ensure specificity." In contrast, Driscoll teaches (in Figures 4, 5, and 6 and in the specification) that the Inverted Repeat (IR) gene of the invention can be approximately 1,400 base pairs or 1,000 base pairs in size. Thus, analyzing these cited references as a combination does not result in an obvious invention. One skilled in the art is left on their own to figure out the proper solution. Driscoll even fails to adequately teach how to make and use their invention for the purposes of suppressing amyloid precursor protein for the treatment of Alzheimer's disease – assuming for a moment this is a proper approach. Even if one assumes that suppression of APP would be an effective treatment for Alzheimer's disease, there is no teaching as to what approximately 1,400 base pair portion of the cited genomic sequences or cDNA sequences for APP should be selected and inserted into an expression vector to yield a therapeutic vector. The genomic sequence for Genbank Accession number D87675 (cited in the Driscoll specification on page 43 line 20) is 301,692 bases in length. Which 1,400 bases out of these 301,692 bases are to be selected for an effective treatment? The cDNA portion of Genbank Accession number is only 2,313 bases in length, but this is still larger than the 1,400 bases exemplified by the Driscoll application. Which portion is to be used? Similarly, the cDNA sequence for Genbank Accession number Y00264 (cited on page 43 line 21) is 2088 bases in length. Which 1,400 bases are to be used?

The actual experiments performed by Driscoll were to show the ability to knock down GFP expression in *C. elegans*. Based on these experiments, they speculate that this too will work in mammalian cells for suppression of APP for treatment of Alzheimer's disease, or suppression of alpha-synuclein for treatment of Parkinson's disease. For example, on page 40 lines 30 through 33 of WO 01/49844 A1, they state "In addition, since dsRNA can inactivate genes in flies, plants, trypanosomes and planaria, *in vivo* directed RNAi could be effective in other organisms." Such a statement without any experimental evidence stretches the bounds of predictability. Examiner rejection must be of that which would have been obvious at the time the invention was made and not through the use of hindsight. Furthermore, the Driscoll speculation was wrong, in that they taught a method of

RNAi (using dsRNA > 30 basepairs in length) that is tolerated in *C.elegans*, but which leads to undesireable side-effects in mammalian cells.

The Examiner should note all the neurodegenerative disease vectors and uses are hypothetical – note the future tense language. It is not clear that the vectors for suppression of APP or alpha-synuclein had actually been built or tested. Obvious to try is not the standard. While Driscoll provides some teaching as to how to make vectors associated with neurodegenerative disorders, Applicants could not find any particular teaching of delivery systems and how to deliver these molecules to particular targets, or any suggestion of the usefulness to consider these factors. Nothing in Driscoll appears to teach or suggests the need to have an intracranial access device, a mapping means, or use of the device with the mapping means to direct delivery of the siRNA.

Before discussing the anatomical maps and coordinates of Paxinos and Cahill, Applicants have submitted amendments to Claim 1 to introduce into several locations that we are referring to treating specific location in the brain of a patient, and that the siRNAs are delivered to this location. These amendments help further distinguish the present invention over the teachings of Paxinos and Cahill.

The Examiner sites the anatomical maps of Paxinos and Cahill as a "mapping means," enabling the skilled artisan to locate predetermined locations of the brain. While the map is a useful teaching tool in gross anatomy, such maps can be applied to dissected brains of cadavers, but are only a starting point for mapping a patient's brain. Moving from a generalized anatomical map, such as Paxinos and Cahill falls short in real life. Placing a delivery device into the live brain of a patient requires exquisite preciseness that can not be obtained from just looking at the Maps and coordinates of Paxinos and Cahill. Applicants mapping means is related to precise live coordinates and structures in a patient that are generated for each individual brain. As you may know, there is an infinite variation of head sizes, shapes, and brain anatomy. Applicant's mapping means is tied to live mapping systems of a patient's brain. The cited maps and coordinates therefore of Paxinos and Cahill fall short of the mark in context of the whole claim.

Applicants believe they have distinguished the cited references from the claimed invention. Use of Xia's et al. green fluorescent proteins is not predictive of treating neurological diseases, and Xia's prediction is only a stated goal or desire. Although expression cassettes for expressing neurodegenerative target siRNAs are described in Driscoll, nothing in the Driscoll reference gives any predictive ability against the neurodegenerative targets. In fact the use of 1 kilobase inserts and the teaching for inhibiting APP teaches away from the actual approach that should be taken. The actual experiments performed by Driscoll were to show knock down of GFP expression in *C. elegans* which leads to at best a hypothesis that this too will work for neurodegenerative targets. Because Driscoll has not actually tested his teaching of using a 1 kilobase APP construct he could not have found the flaws in his approach. Taken on its face, Driscoll actually teaches away from the approach that should be taken. As the Examiner knows, teaching away is a sign of non-obviousness and obvious to try is not the standard. After reading Driscoll, one skilled in the art is left with the paradox of trying something different than what is actually taught by Driscoll. In regard to Paxinos and Cahill references, these references also fail to disclose the claimed mapping means for living patients. Xia's use of a dsRed Expression cassette in cadaver tissue fails to be an equivalent "mapping means."

The Examiner has compiled four references to make the present obviousness rejection. When an invention is analyzed as a combination, the emphasis should not be placed upon its parts.[1] The invention must be considered as a whole and the claims considered in their entirety.[2] There is no legally recognized essence or gist of the invention standard applicable to an obviousness determination.[3] Focusing on the obviousness of substitutions and differences instead of on the invention as a whole . . . [is] a legally improper way to simplify the difficult determination of obviousness.[4] The Examiner has sought to find a

[1] Custom Accessories, 807 F.2d at 959, 1 U.S.P.Q. at 880.
[2] Medtronic, Inc. v. Cardiac Pacemakers, Inc., 721 F.2d 1563, 1567, 220 U.S.P.Q. 97, 101 (Fed. Cir. 1983).
[3] Everpure Inc. Cuno Inc., 875 F.3d. 300, 303, 10 U.S.P.Q. 2d 1855, 1857 (Fed.Circ. 1989); W. L. Gore v. Garlock & Associates, 721 F.2d at 1548, 220 U.S.P.Q. at 309.
[4] Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d 1357, 1383, 231 U.S.P.Q, 81, 93 (Fed. Cir. 1986), cert. Denied, 480 U.S. 947 (1987).

reference to each of the parts of the invention rather than focusing on the Invention as a whole. Xia and Driscoll fail to disclose predictive work for spinocerebellar ataxia type 1, and at times actually teach away from the path that should be chosen. Paxinos and Cahill fail to adequately describe a mapping and delivery means. Examiner rejection must be of that which would have been obvious at the time the invention was made and not through the use of hindsight.[5] Prior art references must be evaluated on what they taught or suggested . . . when the invention was made, not on hypothetical modifications made with knowledge of the invention.[6]

Applicants respectfully request reconsideration of the allowability of Claims 1 and 11-15 under 35 U.S.C. 103(a), and believe these claims are patentable over Xia et al. (2002); in view of Driscoll et al. (WO 01/49844); Paxinos et al. (2001); and Cahill et al. (1995)

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Claims 1, 3, 4, 9, 10, 17, 24, and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Xia et al. (2002); Driscoll et al.; Paxinos et al (200); and Cahill et al, and further in view of Whitesell et al. (1993); Davidson (2004); and Matilla et al (1998). The Examiner indicates it would have been obvious to one of ordinary skill in the art to use the siRNA vectors, as taught by Xia et al. and Driscoll et al. for direct intracranial delivery into the brains of mice and other organisms to reduce the expression of dominant disease causing genes such as mutant ataxin-1 protein and SCA1 based on the teachings of Matilla et al., who teach that a mutant form of ataxin-1 is responsible for the physiological abnormalities associated with SCA1.

The Examiner indicates that one would have been motivated to create such systems for delivering SCA1-targeting small interfering RNA into the brains of mice or rats because Matilla et al teach that SCA-1 has a genetic basis involving the expression of a mutant or toxic form of the SCA1 gene in Purkinje cells of he the brain causing loss of these cells and an ataxic phenotypes (page 5508). Furthermore, the Examiner contends that one would have a reasonable expectation of success given that the combined teachings of Xia et al., Driscoll et al., and Whitesell et al teach that systems for direct delivery of antisense RNA or vectors encoding siRNA (e.g. short hairpin RNA) can be used to effectively reduce gene expression in brain tissues and that the directed delivery with continuous infusion can result in potentially therapeutic levels and extensive brain uptake of antisense oligos (see Whitesell throughout), circumventing the obstacles observed with systemic administration through the blood stream. Furthermore, the Examiner

[5] Panduit Corp., 774 F.2d at 1090, 227 U.S.P.Q. at 342.
[6] Id. At 1095, 227 U.S.P.Q. at 346.

points to Davidson et al. encourage and teach the use of recombinant siRNA-encoding vectors to treat spinocerebellar ataxia type 1 (SCA1).

Xia et al.; Driscoll et al., Paxinos et al., and Cahill et al. were relied on by the Examiner for the previous reasons given above. These references did not specifically teach the use of a catheter or an access port; a siRNA complementary to an mRNA transcript from the SCA1 gene; injection from a syringe into an intracranial access port; or the use of an infusion pump.

The Examiner cites Whitesell for teaching a system for intraventricular administration of radioactively or fluorescently labeled antisense oligonucleotides into rats (pages 4665-6). The rat subjects as containing 22-gauge steel cannula stereotactically implanted in the lateral ventricle (page 4666). The cannula serve as ports, and for purposes of the examination, are considered to represent catheters ("catheter" is defined by the Merriam-Webster OnLine as a tubular medical device for insertion into body cavities to permit injection of fluids.) through which labeled antisense oligos were injected by bolus injection with a Hamilton syringe or continuous injection using a mini-osmotic pump (page 4666). Whitesell et al. report that their study supports the feasibility of continuously perfusing the CNS with therapeutic concentrations of intact antisense oligos, and the possibility of using such therapeutics to target leptomeninigeal and intraparenchymal disease processes (page 4669). The Examiner further contends that because the oligos were fluorescently labeled, Whitesell et al. were also able to determine, or map the location and distribution of the perfused oligos. Thus the Examiner asserts, the oligos themselves, by virtue of their label, comprises a mapping means.

Before addressing the 3 new references being combined with the 4 earlier references, Applicant refer the examiner to their previous arguments as also being dispositive as to Applicants invention as patentable over the art. Examiner now cites the combination of 7 references to make the present obviousness rejection.

The Examiner's reliance on the teachings of Whitesell et al. is also misplaced in this circumstance. Whitesell et al. teaches delivery of anti-sense DNA oligonucleotides to the rat using a 22-gauge steel cannula implanted into the lateral ventricle. While delivery of marked DNA oligonucleotides to the lateral ventricles is interesting, it fails to be predictive of delivering siRNAs for treatment of spinocerebellar ataxia type 1 to the desired targets (deep cerebellar nuclei (dentate nucleus; emboliform nucleus; globose nucleus; fastigial nucleus) and the cerebellar cortex – see Figure 6a and else where in the specification). Note also that Whitesell et al. are delivering oligodeoxynucleotides (ODNs) -- that is, single stranded DNA,

not double-stranded RNA (as needed for siRNA) nor DNA (double-stranded) encoding expression cassettes from which shRNA could be expressed. The fact that phosphorothioated ssDNA isn't so rapidly degraded in CSF does not make it reasonably predictable that dsRNA wouldn't be rapidly degraded by enzymes in the CSF, nor that double-stranded DNA expression cassettes would penetrate brain tissue from the CSF in the manner that Whitesell reported for their short oligos of ssDNA.

Further using the teaching of Whitesell for delivery of antisense oligodeoxynucleotides to lateral ventricle is not particularly useful in treating spinocerebellar ataxia type 1 or any other of the claimed neurodegenerative diseases. Whitesell et al did not test nor teach the administration of antisense oligonucleotides into the brain tissue (or any of the anatomical targets Applicants have specified), but rather the administration of a concentrated solution of antisense oligonucleotides into the cerebral ventricles by continuous infusion (page 4667) (the cerebral ventricles are fluid spaces in the brain). There is no teaching nor means to predict from Whitesell et al., or combined with the other references cited by the examiner, that the concentrations of antisense DNA built up in the CSF would, even chronically, penetrate the brain tissue to yield an effective therapeutic concentration of antisense DNA in the various anatomical regions of the brain tissue that need to be treated, let alone whether or not such antisense DNA is predictive for siRNA. Whitesell et al. further report that the uptake of the antisense oligodeoxynucleotides seen in the brain tissue from oligodeoxynucleotides chronically administered to the cerebral ventricles (i.e. into the CSF) was only confirmed in astrocytes (i.e., the fluorescently labeled antisense oligonucleotides co-localized with glial fibrillary acidic protein [GFAP] positive cells). They indicate that "the identity of non-GFAP-positive cells that accumulate oligodeoxynucleotide (ODN) during infusion remains to be determined" (pg 4668, last sentence of Results section). That is, they do not even explicitly speculate that their delivery method would result in delivery of oligonucleotides into neurons, which must be treated to be effective in treating spinocerebellar ataxia type 1 in the manner of Applicants invention.

In contrast, Applicant specifically teaches the infusion of our therapeutic compounds directly into the targeted brain tissue, and not the cerebral ventricles. Further, moving Whitesell's target to the desired target for spinocerebellar ataxia type 1 using the general anatomical map, such as Paxinos and Cahill, fails in real life to be reasonably predictable from these teachings. Placing a delivery device into the live brain of a patient requires exquisite preciseness. Applicants mapping means is related to precise live coordinates and structures of each individual patient's brain. As you may know, there is an infinite variation of head sizes, shapes, and brain anatomy. Applicants mapping means is tied to live mapping systems of the brain to precise targets using precise siRNAs for specific diseases while the patient is alive.

The Examiner has added the Davidson et al. reference for teaching a method of preparing viral vectors encoding small interfering RNAs for use in gene silencing therapy of genes associated with neurodegenerative disorders, including spinocerebellar ataxia type 1 (SCA1). The Examiner particularly highlights paragraphs 180-185 for this teaching. The Examiner forwards the notion that Davidson et al. contemplate the use of their invention as a method of reducing the expression of a gene product (paragraph 5) such that as that associated with SCA (see claims 23 and 48) and teach the construction of siRNA expression cassettes (paragraph 136-156) and siRNA-encoding recombinant viruses (paragraphs 157-170) for general use in vivo via direct delivery to a mouse brain (paragraph 209).

In regard to the Davidson reference, it is important to note that a lot of the work contained in this patent application was previously published in the Xia et al reference (Inventors Davidson, BL; Xi, H; and Qinwen, M; are co-authors of the Xia et al. publication previously cited. Experimentally, Applicants could not see any major new contributions in Davidson et al., over the previously cited Xia et al. reference. Davidson shows the same reduced GFP expression in the injected hemisphere and thus teaches a system for reducing gene expression in the brain using a vector encoding a small interfering RNA as Xia et al. Davidson et al. as in Xia et al. tested their siRNAs in neural PC12 cell line based on *in vitro* suppression of a eGFP-polyglutamine fusion vector. It is important to point out that Xia et al. did

not measure direct inhibition against the native target, but against an artificially expressed eGFP-polyglutamine fusion sequence. One skilled in the art would not necessarily equate the two. Davidson does list a number of diseases this technology may be useful for, including various spinocerebellar ataxias (SCA1, 2, 3, 6, and 7). However, after the suggestion, no additional teaching of the target to achieve such results is given. Davidson does not per se teach even one siRNA that would be useful for treatment of any of neurodegenerative disease discussed. Thus, the problem still remains, which siRNA sequences out of the thousands of base pair sequences in the relevant genes are to be selected for an effective treatment?

Finally, the Examiner indicates the sequences of Davidson are for general use in vivo via direct delivery to a mouse brain. As previously, discussed in Xia et al., Xia uses a syringe to deliver the viral vectors containing green fluorescent protein as the equivalent of the delivery means. No more is provided in Davidson then in Xia et al. The Examiner uses the fact that Xia uses a dsRed expression cassette, which allows for unequivocal localization of the injection by fluorescence microscopy as being equivalent to the "mapping means." The problem is that the mapping means of Xia et al. and Davidson et al., is generally only for sacrificed patients. In Xia et al., the mice have been sacrificed and are now subject to histology. Xia et al. does not provide an active mapping means to determine delivery of live patients and hence could not be used to treat a neurodegenerative disorder. The mapping means of Xia et al. and Davidson is post-mortem.

The Examiner cites Matilla for providing the motivation to create systems for delivering SCA1 targeting siRNAs into the brains of mice or rats because Matilla et al teach that SCA1 has a genetic basis involving the expression of a mutant or toxic form of SCA1 gene in Purkinje cells of the brain causing loss of these cells and an ataxic phenotype (page 5508). While Matilla is important for what it stands for, reading Matilla, one only learns knocking out SCA1 gene function from embryonic conception does not cause an ataxic phenotype in the developing or adult animal, indicating that the SCA1 disease in humans is not due to a loss of the function of the SCA1 gene or ataxin-1 protein. No suggestion or direction is provided to

suppress the expression of the SCA1 gene in patients as a means of treating the disease, let alone to explore siRNA technology as a means for doing so.

The Examiner has now compiled 7 references to make the present obviousness rejection. As previously stated, when an invention is analyzed as a combination, the emphasis should not be placed upon its parts.[7] The invention must be considered as a whole and the claims considered in their entirety.[8] There is no legally recognized essence or gist of the invention standard applicable to an obviousness determination.[9] Focusing on the obviousness of substitutions and differences instead of on the invention as a whole . . . [is] a legally improper way to simplify the difficult determination of obviousness.[10] The Examiner has sought to find a reference to each of the parts of the invention rather than focusing on the Invention as a whole. Xia and Driscoll fail to disclose predictive work for spinocerebellar ataxia type 1. Davidson's work on shRNA molecules is not instructive as to what siRNAs are useful for neurodegenerative diseases or provide any mapping or delivery means for directed delivery of the siRNAs. Paxinos et al and Cahill et al did not supply the required mapping and delivery means. Work by Matilla et al., was important for the observation that SCA-1 knockout mice at the SCA1 gene locus did not have excessively harmful effects; however, does not teach suppression of ataxin-1 expression in the brain as a treatment for disease, how to make siRNAs for treatment of neurodegenerative diseases or how to locate the appropriate tissue region or deliver siRNAs to the appropriate target. Examiner rejection must be of that which would have been obvious at the time the invention was made and not through the use of hindsight.[11] Prior art references must be evaluated on what they taught or suggested . . . when the invention was made, not on hypothetical modifications made with knowledge of the invention.[12]

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[7] Custom Accessories, 807 F.2d at 959, 1 U.S.P.Q. at 880.
[8] Medtronic, Inc. v. Cardiac Pacemakers, Inc., 721 F.2d 1563, 1567, 220 U.S.P.Q. 97, 101 (Fed. Cir. 1983).
[9] Everpure Inc. Cuno Inc., 875 F.3d. 300, 303, 10 U.S.P.Q. 2d 1855, 1857 (Fed.Circ. 1989); W. L. Gore v. Garlock & Associates, 721 F.2d at 1548, 220 U.S.P.Q. at 309.
[10] Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d 1357, 1383, 231 U.S.P.Q, 81, 93 (Fed. Cir. 1986), cert. Denied, 480 U.S. 947 (1987).
[11] Panduit Corp., 774 F.2d at 1090, 227 U.S.P.Q. at 342.
[12] Id. At 1095, 227 U.S.P.Q. at 346.

Applicants respectfully request reconsideration of the allowability of Claims 1, 3, 4, 9, 10, 17, 24, and 25 under 35 U.S.C. 103(a), and believe these claims are patentable over Xia et al. (2002); Driscoll et al.; Paxinos et al (200); and Cahill et al, and further in view of Whitesell et al. (1993); Davidson et al.; and Matilla et al. (1998).

Conclusion

Applicants respectfully request reconsideration of the allowability of Claims 1, 5, 9-10, 14, 19, and 23-25. Applicants believe they have cured any formal errors in the specification, and have addressed all objections and rejections to the claims, and respectively request the present application be allowed to issue.

Respectfully submitted,

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